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Complicated Soft Tissue Infection with Prepatellar Bursitis Caused by *Paecilomyces lilacinus* in an Immunocompetent Host: Case Report and Review

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Documented *Paecilomyces lilacinus* infections are quite rare. Most reports involve immunocompromised patients or implanted objects. We report the first case of complicated soft tissue infection caused by *P. lilacinus* in an immunocompetent host. The spectrum of infections involving this fungus is reviewed.

Paecilomyces species are widely distributed throughout the environment. They are frequently detected in soil samples (3, 5, 9, 16), decomposing vegetation (29), and as airborne contaminants (22).

Despite its ubiquity, *Paecilomyces lilacinus* remains an uncommon cause of fungal infections in humans. The majority of case reports describe ocular infections (1, 6, 10, 13, 14, 16, 18, 19, 27). Others have implicated *Paecilomyces lilacinus* as a cause of dermatologic infection (2, 8, 15, 28), sinusitis (23, 24), pulmonary mycosis (4), an abdominal wall abscess (26), and fungemia related to an indwelling catheter (29). We describe the first reported case of deep soft tissue infection with bursitis caused by *Paecilomyces lilacinus* in an immunocompetent host. Surgery and prolonged antifungal therapy were required to eradicate the infection.

Case report. A 35-year-old male Caucasian presented to a general internist complaining of pain and swelling below his right knee for 5 days. The patient was employed as an auto mechanic and stated that his pain began after working on his knees on a cement floor. He did not recall any break in the skin or any injury involving a foreign body. A diagnosis of pretibial effusion was made, and fluid was aspirated. A swab culture of the fluid for aerobic bacteria revealed no growth. The patient saw a second physician shortly thereafter, with the same complaints. The area was again aspirated and then injected with a corticosteroid. Cultures were not obtained.

Although his symptoms improved briefly, pain and swelling returned 2 months later, at which time the patient was evaluated by an orthopedic surgeon. A radiograph of the knee was normal, and a clinical diagnosis of prepatellar bursitis was made. One week later, he was examined by a rheumatologist, who aspirated a fluctuant pretibial lesion. Four milliliters of purulent material contained 183,000 polymorphonuclear leukocytes per mm^3, 30,000 erythrocytes per mm3, and a glucose level of 4 mg/dl. Gram's stain revealed many polymorphonuclear leukocytes but no organisms. Treatment with oral cefaclor was initiated. Cultures for aerobic bacteria and mycobacteria were subsequently negative, but a mould was isolated from the aspirated pus. The patient's signs and symptoms did not improve with the antibiotic, and he developed a temperature of 101 to 102°F (~38.5 to 38.7°C). Five days later his antibiotic treatment was empirically changed to oral dicloxacillin.

After another week of antibacterial therapy, radiographs of the right knee, tibia, and fibula were interpreted as normal. At that time, another aspiration of the site was performed, yielding 1.5 ml of fluid containing 2,600 leukocytes per mm^3, 97% of which were polymorphonuclear leukocytes, and 21,300 erythrocytes per mm^3. Bacterial and mycobacterial cultures were negative, but fungal cultures of the aspirate again grew a mould morphologically identical to the first isolate.

The patient was then referred to an infectious disease specialist. He appeared well and in no acute distress but walked with a tentative gait that was limited by pain in his right leg. He was afebrile. The right lower extremity contained a horseshoe-shaped area of warmth, erythema, induration, and tenderness anteriorly just below the knee. The knee joint itself exhibited full range of motion without effusion. There were no ulcerations or evidence of lymphangitis. An erythrocyte sedimentation rate was 7 mm/h. Antibodies to human immunodeficiency virus were not detected.

A magnetic resonance imaging scan, performed 2 weeks after the second aspiration, revealed extensive superficial and deep soft tissue involvement. The patient elected to pursue a course of leg immobilization and oral fluconazole (200 mg per os daily) rather than immediate surgery.

The microbiology laboratory identified the mould isolate as a *Penicillium*/*Paecilomyces* species, suspicious for *Paecilomyces lilacinus*. The identification of *Paecilomyces lilacinus* was subsequently confirmed (Fungus Testing Laboratory, San Antonio, Tex.).

Despite continued oral antifungal therapy, a dull ache and swelling persisted in the leg, and plans were made for debridement. He was admitted to the hospital 4 months after he was first evaluated by a physician and placed on intravenous miconazole because in vitro susceptibility testing indicated that the isolate was resistant to fluconazole. Three days later the right anterior tibial soft tissue was debrided. Multiple fragments of soft, pink tissue, measuring approximately 2.0 to 5.0 by 1.0 to 2.0 by 0.5 to 1.5 cm, were excised. No gross evidence of extension to bone was noted; therefore, the surgeon elected not to perform a bone biopsy. Microscopically, the connective tissue was replaced by confluent caseating granulomas. Palisading of epithelioid macrophages was prominent, and multinucleated giant cells were present. Gomori's methenamine silver stain demonstrated septated hyphal fragments, some of

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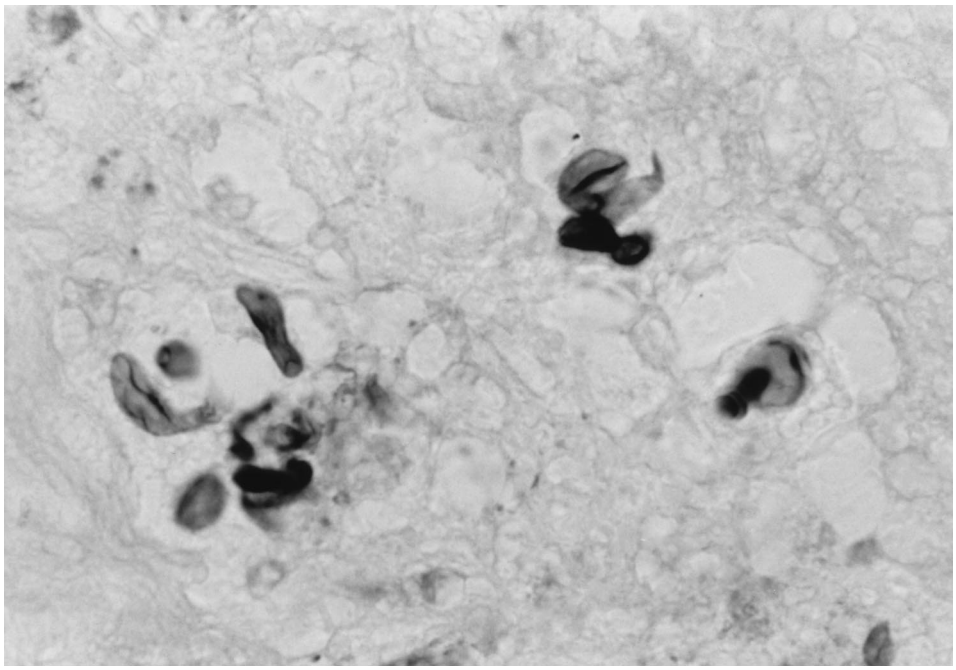

FIG. 1. Distorted and swollen hyphal fragments are present in the wall of a caseating granuloma (methenamine silver stain). Magnification, ×400.

which were swollen (Fig. 1). Purulent inflammation was not observed. Acid-fast stains were negative.

The patient developed severe phlebitis from miconazole, and therapy was changed to oral ketoconazole (400 mg daily). He was discharged 1 week after admission.

At follow-up approximately 3 weeks after surgery his wound was healing very well. He denied any fever or chills but did report an occasional achiness in the leg. The patient's overall signs and symptoms were greatly improved, and he was beginning physical therapy while continuing to take ketoconazole. Plain films of the knee and upper tibia, obtained approximately 1 month after discharge, were normal.

A repeat magnetic resonance imaging scan performed approximately 8 months after initial presentation was normal without evidence of osteomyelitis. One week before that scan the patient had stopped taking ketoconazole. Although he experienced some chronic leg pain distal to his incision, he continued physical therapy and eventually returned to work. A follow-up visit approximately 1 year postsurgery found him to be pain free with no further complications.

Microbiological findings. *Paecilomyces lilacinus* was isolated on two occasions from aspirates of the right infrapatellar bursa obtained 12 days apart. The fungus produced white, floccose colonies within 3 days on Sabouraud dextrose agar with and without cycloheximide and chloramphenicol. After 4 days as conidia began to form, the mycelium developed a lilac-rose-red color, which became deeper as the colonies aged. Pigment production was enhanced by placing the fungus on potato flakes agar (21) and Czapek agar (29). The reverse side of the colony was nonpigmented. The isolate was somewhat adherent to the agar.

Microscopic examination revealed branched phialides organized as a "penicillus," initially suggesting a *Penicillium* species. On further examination with calcofluor white, numerous phialides that possessed long, constricted or tapered necks, suggestive of *Paecilomyces* species, were observed. Primarily oval conidia appeared in elongated chains. Conidia consistently measured 3.0 by 2.0 μm (Fig. 2). On the basis of these microscopic characteristics and the lilac pigment, *Paecilomyces lilacinus* was identified.

Susceptibility testing was performed (Fungus Testing Laboratory) by the macro broth dilution method. The isolate was resistant to fluconazole, itraconazole, and amphotericin B (MICs of >64, >8, and >16 μg/ml, respectively), and susceptible to ketoconazole and miconazole (MICs of 1 and 0.5 μg/ml, respectively).

Discussion. *Paecilomyces lilacinus* was known as *Penicillium*

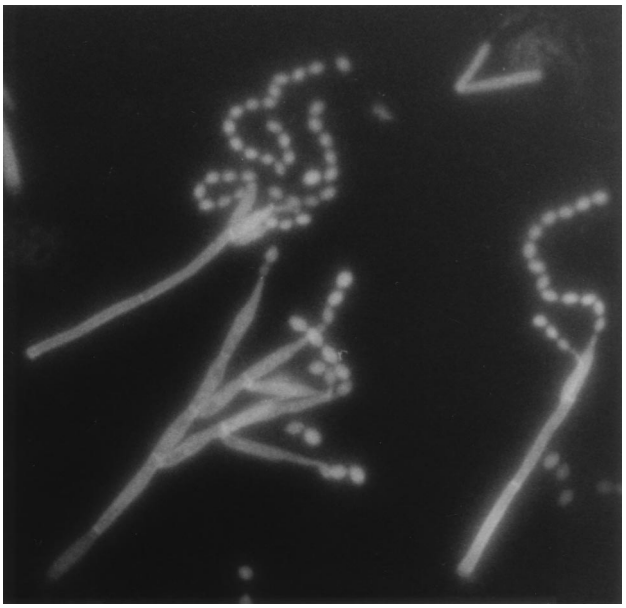

FIG. 2. Long, tapering phialides with extended chains of oval conidia, typical of *Paecilomyces lilacinus* in a Calcofluor white preparation. Magnification, ×400.

lilacinum (20) until 1974, when Samson proposed that it be transferred to the genus *Paecilomyces* (25, 29). Morphologically, the fungus closely resembles members of the genus *Penicillium*, and disagreement continues to exist among experts as to the correct taxonomic designation (29). The diagnostic difficulty is reflected in numerous case reports that describe an initial laboratory identification of *Penicillium* species before a final report of *Paecilomyces lilacinus* was issued (15, 19, 26, 27, 29).

Despite being prevalent in the environment, documented fungal infection by *Paecilomyces lilacinus* occurs very rarely. This case represents the first report of complex soft tissue infection with bursitis caused by this fungus in an immunocompetent host. Several recently published reports (26, 29) and the case we describe, suggest that *Paecilomyces lilacinus* may be emerging as an important pathogen.

The bulk of reported *Paecilomyces lilacinus* infections involve the eye. Endophthalmitis has been described by several investigators (10, 13, 16, 18, 19). Twelve patients became infected when contaminated intraocular lenses (13, 18, 19) were unknowingly implanted. This outbreak illustrates the potential of this fungus to cause severe morbidity, as the majority of eyes involved were not salvageable, and its ability to survive commercial sterilization methods. *Paecilomyces lilacinus* has also caused several episodes of keratitis (14, 27), an infected corneal transplant (6), and an orbital granuloma (1). Vision was improved in the patients with keratitis after prompt medical intervention. A combination of aggressive antifungal therapy and a second transplant led to the resolution of the infection in the patient reported by Gordon and Norton (6). Agrawal et al. reported resolution of the orbital infection with excentration, but dissemination to neighboring tissue occurred despite surgery and amphotericin B therapy (1).

Dermatologic infection with *Paecilomyces lilacinus* constitutes the next largest group of published reports. Jade et al. described a case of a deep cellulitis in an immunocompromised patient in which a favorable outcome was achieved only after combination therapy with amphotericin B and flucytosine (8). Castro et al. reported an infection caused by *Paecilomyces lilacinus* that was localized to the left forearm in a renal transplant patient. Their patient was cured with oral griseofulvin (500 mg/day) (2). Murciano et al. reported a cutaneous infection with *Paecilomyces lilacinus* in a young girl with leukemia (15). This patient's course was complicated by persistent neutropenia, and she subsequently died. It was not clear whether dissemination had occurred because an autopsy was refused. Takayasu et al. described a case of cutaneous mycosis caused by *Paecilomyces lilacinus* in an immunocompetent host (28). The fungus was repeatedly isolated from biopsy specimens taken from lesions on the patient's left cheek, and hyphal elements were observed in tissue sections. The lesions were greatly reduced in number with oral griseofulvin.

Additional accounts of *Paecilomyces lilacinus* infection include two reports of chronic maxillary sinusitis (23, 24), both cured with surgical debridement, and a report of pulmonary mycosis (4) which required amphotericin B therapy. All three infections occurred in immunocompetent hosts. Tan et al. described a recent case of catheter related fungemia in an immunocompromised pediatric patient (29). Removal of the catheter and treatment with amphotericin B resulted in a cure. Another recent report, by Silliman et al., implicates *Paecilomyces lilacinus* as the etiologic agent of two abdominal wall abscesses in a child with chronic granulomatous disease (26). Although the infection appeared to respond well to amphotericin B therapy, the child died 4 months later of an unrelated infection. *Paecilomyces lilacinus* has also been reported as a pathogen in animals (5) and insects (29).

Paecilomyces species other than *Paecilomyces lilacinus* also cause occasional infection (9, 22). The majority of these involve *Paecilomyces variotii*. Henig et al. described a case of *Paecilomyces* infection of the lacrimal sac, in which the species identification was not determined (7).

Given the ubiquity of *Paecilomyces lilacinus* in the environment (3, 9, 20, 22, 29), it is likely that the patient described in this report acquired his infection through minor trauma to his knees while working as an auto mechanic. Although he did not remember any puncture wounds or breaks in his skin, he had spent considerable time on his knees before development of symptoms.

It is interesting to note that the patient's knee had been manipulated twice, including injection with a corticosteroid, before *Paecilomyces lilacinus* was isolated. Although introduction of the fungus during aspiration or injection seems unlikely in this case, that possibility cannot be eliminated.

Numerous strains of *Paecilomyces lilacinus* are capable of producing potent mycotoxins (11, 12). Leucinostatins derived from cultures of the organism are highly toxic to experimental animals and appear to have had a direct impact on the tissue inflammatory response. Inoculation of leucinostatin directly into the cornea of a rabbit resulted in abscess formation. These findings suggest that toxin production by *Paecilomyces lilacinus* may be an important virulence factor (11, 12).

The therapy of invasive fungal infections usually includes the removal of any foreign bodies or medical devices, debridement or excision of infected tissue, and/or treatment with antifungal chemotherapeutic agents. Susceptibility testing of moulds has not yet been completely standardized or validated. A standard macrotube MIC test has been proposed by the National Committee for Clinical Laboratory Standards (17) and was used by the reference laboratory for this isolate. For infrequent pathogens, such as *Paecilomyces lilacinus*, construction of reliable interpretative criteria for susceptibility tests is particularly difficult.

In general, *Paecilomyces variotii* is susceptible in vitro to common antifungal chemotherapeutic agents, whereas *Paecilomyces lilacinus* is resistant to amphotericin B and flucytosine but susceptible to imidazole compounds. Despite in vitro susceptibility data, several reports already mentioned describe a positive outcome when amphotericin B was administered. Explanations for this discrepancy may include strain differences of *Paecilomyces lilacinus*, responses to surgical or local measures independent of amphotericin therapy, or that criteria for defining interpretation breakpoints need further refinement. Oral griseofulvin was also used successfully in two patients described previously (2, 28).

In our case, cure was achieved with a combination of surgical excision of infected tissue and prolonged administration of imidazole compounds to which the isolate was susceptible in vitro. Treatment with fluconazole alone (to which the isolate was ultimately determined resistant in vitro) did not effect a clinical cure, although the mould could not be recovered from infected tissue at the time of surgery.

Although infection is uncommon, it is important for clinicians and microbiologists to consider the potential pathogenicity of any isolate of *Paecilomyces lilacinus* within the context of the clinical factors. It is likely that this fungus will continue to be implicated as a cause of invasive infection. Multiple isolates of a fungus from the same specimen and/or patient increases the likelihood that the isolate is clinically significant. Demonstrating morphologically compatible fungi in tissue sections authenticates the diagnosis.

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